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**"TRIC AGENT" URETHRITIS: A REPORT OF THE SEROLOGICAL
FLUORESCENT ANTIBODY AND ASSOCIATED FINDINGS**

by

CDR T. S. Kent, MC, USN

Bureau of Medicine and Surgery, Navy Department
Project MF099.01.01.01

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ADMINISTRATIVE INFORMATION

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ABSTRACT

The relationship between Trachoma-Inclusion Conjunctivitis agents (TRIC Agents) and Non-Specific urethritis (NSU) was investigated. The results of complement fixation and immunofluorescence studies using a "group" and a "type-specific" antigen/antiserum are presented in detail, as well as other associated clinical and laboratory findings related to a routine evaluation of urethritis. It was shown that one or more TRIC agents probably account for a much larger percentage of "NSU" cases than previously thought. There appears to be a definite interrelationship between TRIC urethritis and epididymitis in young adults, and possibly with Reiter's Syndrome. Further investigation of these relationships should certainly be done. (A protocol for such a study to be conducted at USNH, San Diego is being prepared for submission.)

TABLE OF CONTENTS

Abstract	iii
Summary	vii
Introduction	1
Methods and Materials	2
Results	6
Discussion and Conclusions	16
References	21

LIST OF TABLES

- I. Clinical Groups and Corresponding CFT results
- II. Group IV Controls: Results of urinalyses and CFT's in three sub-groups (102 cases)
- III. Results of Fluorescent Antibody Tests
- IV. Morbidity Findings: Groups I and II
- V. Findings on Prostate Examination and correlation to CFT results
- VI. Complement Fixation Titer Responses to OA Antigen:
 - (a) Time of appearance, level and distribution of titers becoming reactive for the first time
 - (b) Time of occurrence of "Peak" titer levels among cases presented in Table VI (a)
 - (c) Results of cases having "reactive" CFT's (at any level) when initially seen

SUMMARY

A 10 month study of the relationship of TRIC Agents and NSU was conducted aboard the USS Hunley, in Holy Loch, Scotland, and coordinated with the Belvedere Hospital Virology Laboratory. Personnel of Submarine Squadron-14, with an average strength of approximately 1800 men, comprised the study population. The relative value of the study was greatly enhanced by the control that could be placed on personnel movements to and from the ship.

Of the 463 patients included, there were: 107—NSU; 51—Gonorrheal urethritis; 22—asymptomatic abacterial pyuria; and 283 controls.

In addition to the usual bacteriological studies performed in all cases of urethritis, serological and fluorescent antibody tests for the Trachoma-Inclusion Conjunctivitis Agents were performed. Type specific reagents were prepared from the LB₄ strain and the group tests utilized reagents from the Ovine Abortion strain for C.F.T.'s and standard LGV strain for F.A. tests. The titer responses and results of the F.A. tests were presented in detail.

A previous study had reported the type specific CFT for the LB₄ strain to be positive in a large number of cases, but the incidence had gradually decreased and then disappeared completely during the 2nd month of the current study. Only 5 cases with an LB₄ titer response at any level were found, though the number of NSU cases did not decrease and the group antigen tests remained positive.

It was shown that significant C.F. titers to the OA group antigen were present in 40 to 50% of the cases in Group I, II, and III. The control group (IV) revealed only a relatively small percentage of cases with reactive titers—and there was a very high incidence of pyuria in these patients. It is thought that many cases are overlooked because of the failure to recognize or to accept the fact that there is an asymptomatic form of this disease called "NSU." Abacterial pyuria is the only finding and is usually discovered incidental to other examinations.

C.F. titer levels of 16 are probably often "positive," and even some at lower dilutions also, when all the clinical aspects of a case are considered. Many cases probably require repeated exposures to the infectious agent before a titer rise occurs to a high enough level generally considered positive.

Fluorescent antibody studies offer a method of rapid diagnosis of TRIC urethritis from urethral smears. With improvement of techniques and preparation of reagents (antisera) this procedure should prove to be the most reliable.

"Non-specific" epididymitis, which is fairly common among the younger age group in the Navy, is probably a complication occurring mainly among the "inapparent" or very mild cases of TRIC urethritis that go untreated. This association between TRIC agents and epididymitis certainly deserves further evaluation.

"TRIC AGENT" URETHRITIS: A REPORT OF THE SEROLOGICAL FLUORESCENT ANTIBODY AND ASSOCIATED FINDINGS

INTRODUCTION

Non-specific urethritis (NSU) is a term used collectively for any condition of unknown etiology that causes inflammation of the urethra. It is "diagnosed" by the exclusion of gonorrhea and other known causes of urethritis, and the majority of cases are generally considered to be of venereal origin.^{7, 32, 35} The symptoms may closely mimic gonorrheal urethritis occasionally, but they are usually mild and as Harkness so aptly stated, these "mild signs and symptoms are often overlooked, minimized, misdiagnosed, and wrongly treated."

Though various etiological theories have been proposed,^{2, 28, 35} none have been generally accepted as the cause of the majority of cases. It would appear that sub-microscopic organisms are the most probable causative agents, namely pleuropneumonia-like organisms (PPLO) and/or viruses. Currently, the most notable among these agents are the "T-strain" PPLO³⁵ and some of the Trachoma-Inclusion Conjunctivitis group of organisms (TRIC Agents).^{3, 14, 20}

Viruses were implicated with non-specific urethritis (NSU) as far back as 1909 when Linder demonstrated initial and elementary bodies indistinguishable from those of inclusion conjunctivitis. In subsequent studies of this agent as reported by Harkness,³² the main emphasis was placed on the ocular manifestations. Sporadic reports of "inclusion urethritis" continued, but the incidence was considered to be small.^{7, 32}

There has been a revival of interest concerning the association of TRIC Agents and NSU, especially in the United Kingdom, since Jones and his associates reported a case of blindness in a newborn infant with conjunctivitis in which the LB₄ strain of TRIC was isolated from the infant's eyes and from the genital organs of both parents. They also have reported several other cases of newborn

conjunctivitis with concurrent isolation of TRIC from the infants' eyes and the mother's genital tract^{8, 12, 14} and similar reports have been published by Mordhorst^{16, 17}. A subsequent study in the West of Scotland by Pasienczny and Sommerville²⁰, using LB₄ type specific antigen revealed reciprocal complement fixation titers to be positive (1:32 or greater) in 25% of 200 cases of abacterial urethritis attending venereal disease clinics in Glasgow. It was suggested that a positive titer may actually be lower than the level of 32 utilized here, but only experience would tell. The finding of low antibody titers in cases with positive isolation of various TRIC strains have been reported by Barnes,³ Jones et al,¹⁴ and Mordhorst.¹⁷

TRIC Agents belong to the Psittacosis group of organisms (Psittacosis, Lymphogranuloma venereum, Trachoma and Inclusion Conjunctivitis) and are sometimes called the "PLV" group or "PLT" group. Initially, they were considered to be large viruses, but recent studies of the chemistry of the cell wall, electron microscopy of living cells, the metabolism of the purified particles, and the action of antibiotics place the group with the bacteria.³⁸ Bergey has given them the family name of *Chlamydiaceae*, but this has not been well accepted. Zinsser's *Microbiology* has suggested the name "bedsonia" group, and it is appearing frequently in the literature.

Though placed with the bacteria, they exhibit obligate intracellular parasitism.³⁸ As a group they can be propagated in eggs, but for some reason the inclusion conjunctivitis strains affecting humans have been more difficult to isolate than trachoma.^{10, 16, 18} Isolation of other TRIC agents from animals with natural and experimental disease has apparently been much easier.^{9, 19}

Latency is a prominent feature of the bedsonia, and the organism can remain in infected cells for long periods without apparent

cell damage.^{33, 34, 38} It appears to involve the maturation phase within the host cell and can be interrupted by various antibiotics and drugs, and by cell nutrition.^{33, 38} The coexistence of latent infection and host antibodies is typical of the psittacosis group according to Jawetz, Melnick, and Adelberg.³⁴

Serologically, all the bedsonia have certain common and type specific antigens. The common antigen will cross react with other members of the group in varying degrees, but will give the highest complement fixation titer when it reacts with antibodies against its own strain, or another closely related strain. Even the "type specific" antigens of various strains have been shown to exhibit some ability to cross react with other strains.^{9,19,31} Fraser and Berman,⁹ in an outstanding publication on type specific bedsonia antigens obtained from various types of diseases in animals were able to demonstrate seven (7) distinct serological subgroups among the 14 antigens tested.

Pasienczny and Sommerville's interesting investigation of an "outbreak" of NSU due to the LB₄ strain of TRIC Agent fostered the idea for a further evaluation of the problem, utilizing the personnel assigned to Submarine Squadron FOURTEEN, the advanced Polaris Submarine Base in the Holy Loch by Dunoon. The squadron was composed of various ships including the submarine tender, USS HUNLEY (AS 31), a floating dry dock, USS ALAMOS (AFDB 7), and the various submarines that were periodically moored alongside. All the units had an average primary strength of 1450 men and a secondary strength of 400-500 men. This population was almost perfect for the study and rather unique with regard to control of personnel movements because: (1) the units of the squadron were all anchored in the Holy Loch and the only access to the group of ships was by motor launch. (2) Medical quarantine during the acute stages of disease was easily managed due to the strict security regulations in force, since each person coming aboard or departing was checked at the Quarterdeck. (3) The patients were readily available for follow-up studies to assure they

were free of disease and to receive further treatment if required.

The study was coordinated between the Hunley Medical Department and the Belvedere Hospital Virology Department under the direction of Dr. R. G. Sommerville. All basic diagnostic procedures and patient evaluations and treatments were conducted by medical personnel aboard the USS HUNLEY. Specimens for serological and immunofluorescence (FA) studies were collected aboard ship and were delivered to the virology laboratory for testing.

METHODS AND MATERIALS

Clinical and Bacteriological:

The investigation covered the period from April 1965 through January 1966. Consecutive cases presenting at sick call with signs and/or symptoms of urethritis or other lower genitourinary tract disease (prostatitis, epididymitis, etc.) were interviewed and examined by the author. Interviews with those cases occurring on submarines at sea were obtained later and special arrangements were made for the collection and storage of serum specimens. All cases were included in the study **except** those with a history of venereal disease in the prior four (4) months and those due to receive transfer orders in less than ten (10) days. No patient was used more than once unless at least six (6) months had elapsed since the original case, and he was free of clinical or laboratory evidence of disease for the prior three (3) months, (except the Group IV controls who later developed urethritis, etc.).

There were 463 male patients included in the study who were segregated into groups according to the clinical diagnosis as follows:

Group No.	Description	No. of Cases
I	Non-gonococcal urethritis, and other lower genitourinary tract conditions.	107
II	Gonococcal Urethritis	51
III	Asymptomatic, Abacterial Pyuria	22
IV	Control Cases	283

Groups I and II: A listing was maintained on consecutive cases presenting at sick call with symptoms of urethritis (of any type) or other lower genitourinary tract conditions (i.e., prostatitis, epididymitis, prostaticorrhea, etc.). Even the most minimal of urethral symptoms ("itching," "paresthesias," or a "morning tear") were included here when associated with pus or shreds in the first glass of a two-glass urine specimen. Patients with a urethral smear positive for *N. gonorrhea* were started on treatment and were listed in Group II.

Group III: These were cases with "asymptomatic, abacterial pyuria" found as an incidental finding during the course of a routine physical exam or an evaluation of another medical problem not related to the urinary tract. Other criteria included: no history of venereal disease during the prior four (4) months; a two-glass urinalysis with pus and shreds in the first glass, and the second glass specimen showing a negative culture and microscopic examination.

Group IV: This group of controls was comprised of patients with no urinary complaints and no history of venereal disease in the prior four (4) months. These patients were added to the group periodically throughout the entire span of the study. The cases were derived from a group of blood donors, various routine physicals (premarital, annual, reenlistment and radiation preplacement), patients presenting to sick call with various complaints, volunteers, etc. Each patient was either interviewed personally or was given a detailed questionnaire to complete. Of the patients included with acute illnesses, 34 of them had respiratory complaints and many of them were admitted to the ward for treatment. Ten (10) of the patients were from a nuclear submarine that had an outbreak of *Mycoplasma pneumoniae*.²² Two (2) of Sawyer's patients could not be used as controls because they also had recently had NSU and were already included in Group I. Complement fixation tests were performed for antibodies to the following potential respiratory disease agents: Influenza A, B, & C, Adenovirus, Respiratory Syncytial virus, Parainfluenza

3, Psittacosis, *Rickettsia brunetti*, and *Mycoplasma pneumoniae*.

Laboratory Procedures:

The "intraurethral loop" method was used for collecting specimens for smears and cultures. Gonorrhea was diagnosed by gram stained smears and confirmed by culture using the standard candle-jar technique with chocolate agar media initially and then with Thayer-Martin media during the last three (3) months of study. The diagnosis was further documented by the oxidase test and colony gram stains. A diagnosis of non-specific urethritis was not made until a minimum of two (2) and preferably three (3) consecutive daily smears and a culture were reported as negative for *N. gonorrhea*. All gram stained smears were labeled and kept on file for future reference if needed in controversial cases.

Blood agar and Eosin—Methylene—Blue (EMB) cultures were made on a majority of the cases of NSU and especially if other types of intracellular organisms were a prominent finding.³² All the cultures were usually repeated on the third day in such cases; and as time and workload permitted, occasional attempts were made to identify the specific organisms with differential media and sugar fermentations, etc.

When there was a history of minimal or no noticeable urethral discharge and with cases of asymptomatic pyuria, the patients were instructed to report to the laboratory for further test prior to urinating upon arising the following morning. Intraurethral loop smears and cultures were attempted and were sometimes aided by transferring a loop full of sterile Phosphate Buffered Saline (PBS) into the urethra. A "two-glass" urinalysis (for gross shreds and microscopic pyuria) and a midstream urine culture were performed in these cases.

Prostate Examinations: These were performed on Group I and III patients initially, and to follow progressive changes (if any) a sketch and description of the findings were made in the chart. Massages were not done on Group I patients until the post-treatment follow-up visit in 10-14 days at which time a

two-glass urine specimen was obtained and the patient was asked not to completely empty his bladder. The massage was performed and a wet smear of the secretions was examined microscopically. If none were present, the "3rd glass" urine specimen was obtained to collect any prostatic secretions expressed into the urethra. Gram stains were performed on the secretions if indicated by significant pus in the specimen.

Treatment:

Non-Specific Urethritis — Oxytetracycline and occasionally tetracycline 500 mg. every 6 hours for 9 days was used in all but 9 cases (Declomycin (2), Oxytetracycline and Gantrisin (1), Gantrisin (5), Furadantin (1)) for the initial course treatment. Various agents from Kynex, Gantrisin, Declomycin, Furadantin or a repeat course of the original drug were used in cases with recurrent symptoms. Cases with persistent or recurrent pyuria at 3-4 weeks were treated as though they were essentially a new case. After approximately 3 to 4 months, refractory cases were referred to Lakenheath Air Force Base Hospital for Urological evaluation.

Gonorrhea—Penicillin 600,000 units twice daily for 5 days or once daily for 10 days were the two (2) treatment regimes used. At the termination of the study, the treatment was changed to 2.4 million units of Aqueous Penicillin G. in a single dose, and repeated in 48 hours if needed. Tetracycline was used for patients who were sensitive to penicillin. The dose was 500 mg. every 6 hours for 5 to 7 days, and, one medical officer used 500 mg. intramuscularly followed by 500 mg. every 4 hours for a total of 8 doses.

Non-specific urethritis—A patient was considered cured and released from treatment if (1) he remained asymptomatic for a period of six (6) weeks from the date of his last symptoms or treatment whichever was later; (2) a two-glass urine specimen at 4 and 6 weeks revealed less than 6-8 WBC's and very few shreads in the 1st glass, and the 2nd glass specimen was negative for pus and bacteria; and (3) the prostate exam was within normal or borderline limits or at least status quo.

Gonorrhea—The criteria for a cure in these patients were: (1) no clinical evidence of a persistent urethral discharge (unable to "strip a tear" from the urethra), a history that the original discharge had cleared under treatment within 48 hours (and at most, 72 hours), and that there had been no subsequent genitourinary symptoms; (2) bacteriological proof of cure by finding no *N. gonorrheal* organisms on a culture and smear obtained at least 4 days after termination of antibiotic therapy and collected as previously described. The intraurethral loop specimen is more important here, and even without an exudate, the "bare" loop was streaked on the culture plate and the process repeated at least once after the patient had "stripped the urethra;" (3) two-glass urinalysis is obtained at the time the culture and smear were collected and then repeated again in 10-14 days. Shreads and more than 8-10 WBC's prompted the collection of repeat smears and cultures. If the initial post treatment studies proved negative for *N. gonorrhea*, the patient was removed from medical quarantine, but not discharged from follow-up.

Pyuria: The definition of "significant pyuria" is quite variable, but not as controversial as the subject of pus in the prostatic secretions.^{7,35} There are many factors to consider besides the number of pus cells "reported," and only those pertinent here are mentioned. A "mild" (1+) pyuria for the purposes of this study means 8-12 WBC's per high-dry field, and 6-8 WBC's/HPF are "equivocal." Urinalyses falling into these categories were not infrequently the heralding sign of recurrent symptoms or occasionally a new case who reported for a physical exam before the symptoms of urethritis actually developed a few days later. Another significant item that is occasionally overlooked is the relationship of urine specific gravity and the amount of pyuria. A "few WBC's" (4-5) in a markedly dilute urine has been reported as "many mobile bacteria," and "loaded with WBC's" in a specimen collected only 3 to 4 hours later. The type of illness suspected can cause variations — as in this study, a urine report of "a few shreads and 3-4 WBC's/HPF" on a "random specimen"

could show a latent or subclinical G.U. problem if the urine is differentially collected as a "multiple glass" specimen. So, the definition of "significant pyuria" is "relative" to the conditions of the case in question.

Miscellaneous:

Contact Interviews: Nearly all of the venereal disease contact interviews were conducted by one of two senior hospital corpsmen who had received additional training in V.D. control. In each case in Groups I, II, & III an attempt was made to extract the number of different sexual contacts and/or the frequency of contacts with the same consort in detail by chronological listing for at least the two (2) previous months prior to the onset of symptoms. Additional, but approximate data was also obtained as far back as six (6) months or more. These results were all reviewed by the examining medical officer and were filed in a safe after the P.H.S. Epidemiological Reports were completed on those cases proven to have gonorrhea.

Medical Quarantine: All patients suspected of having a venereal urethritis were immediately sent to the laboratory for an initial smear and were then interviewed and were placed on medical quarantine until a diagnosis was made. The cases with NSU were then released from quarantine, but patients with gonorrhea were kept aboard ship until it was proven they were indeed free of disease.

Virological:

Fluorescent Antibody Tests: Complementary smears of urethral discharge were prepared on fluorescence-free microscope slides, fixed in methanol for 10 minutes, allowed to air dry and stored at 4°C pending transportation to Belvedere Hospital. The tests were made for a group antigen (LGV), a strain specific antigen (LB₁), and an occasional sporadic check for Saudia Arabia strains (SA₁ & SA₂). Hyperimmune Rabbit Anti-TRIC serum and FITC coupled Anti-Rabbit serum were alternately applied, incubated at 37°C for 20 minutes, washed with phosphate buffered saline and allowed to air dry prior to examination with a fluorescent microscope. Four (4) to seven (7) epithelial cells with

intracytoplasmic fluorescent inclusions were considered positive.

This part of the study was the most difficult to coordinate and standardize. The main problem was the preparation of poor quality smears and was augmented by the lack of personal communication between the personnel collecting the specimens and the technician who was actually performing the tests at the virology laboratory. During a conference midway through the study, it was learned that most of the FA smears submitted and reported as "negative" had been read as such because they were of such poor diagnostic quality—mainly as a result of being too thick with pus cells, obscuring the epithelial cells and having too much non-specific fluorescence. Further collection of FA smears was temporarily suspended and two (2) of the laboratory technicians aboard USS HUNLEY were sent to the virology laboratory at Belvedere Hospital for two (2) weeks basic indoctrination in virological collection methods and laboratory techniques. Subsequently the technician performing the FA test graded each smear for quality and gave pertinent explanatory remarks with the report. After a period of technique evaluation, the following modifications to the collection procedure were made: (1) in cases with a scanty or no discharge, the transfer of the intraurethral "loop specimen" to the slide was facilitated by placing a loop of sterile PBS in the urethra; (2) when the discharge was thick and copious, the specimen was collected **post voiding** or a drop of PBS was placed on the slide to disperse the cells; (3) and more important, the two (2) specimen areas on the slide were immediately checked microscopically with high-dry magnification for the presence of an adequate number of epithelial cells and satisfactory dispersion of all cellular elements prior to excusing the patient. The thin, mucoid discharges were the easiest to smear because they often had nearly as many epithelial cells as pus cells.

Serum Complement Fixation Tests for TRIC Agent: Acute and convalescent sera collected on all cases suspected of having diseases or conditions pertinent to this study

and "paired sera" on all but one (1) subgroup of the control patients. The specimens were tested for antibodies to the group antigen of the Ovine Abortion (OA) strain and to the type specific antigen of the LB₄ strain. The serum was separated from the clot as soon as possible and temporarily stored at -4°C pending transportation to Belvedere Hospital. It was then divided into aliquant parts, a small one for "working stock" and the other for the "master file" storage at -70°C. The reciprocal, cold overnight complement fixation test and the procedure for preparation of the antigen has been previously described.²⁰

Follow-Up Studies: The greater majority of the patients did quite well in keeping their appointments for follow-up studies. Though some would forget, they would respond when reminded by phone. During the first 3-4 weeks an attempt was made to see the patients at 7-10 day intervals at least, and actually the majority reported weekly. In group I, the actual frequency of serum collections was as follows: every 7-10 days for 6-8 weeks (73% of cases); at least 3 sera, including acute, 2-4 week and 6-8 week specimens (13% of cases); the remainder of cases having at least 2 sera, but with 5% being less than optimal for "acute and convalescent" sera. The collection of the serum specimens in groups II and III was almost comparable to that of group I. It became routine to leave a urine specimen on the morning of their appointment and to return later to have their blood collected for the complement fixation test (CFT) or to see the medical officer. The results of the urinalyses were checked by the medical officer later, and those patients requiring further evaluation were notified. The author tried to see each patient at least every 2 weeks to take an interval history regarding G.U. and other symptoms, new sexual contacts, alcohol intake, etc. A portion of the group I patients were given prostate exams during these visits and others were checked only if symptoms, etc., warranted. After the first 3 weeks, the patients were checked at less frequent intervals until they met the criteria for a cure and were released from further follow-up. Some patients with persist-

ently high C.F. titers were seen every 2-4 weeks for re-evaluation over an extended period of time. As stated previously, patients refractory to treatment were referred for urological evaluation. At the termination of the study, follow-up evaluation was continued for those patients requiring it, and the results were included here.

RESULTS

General:

The age of the patients in Groups I and II ranged from 18 to 45 years—86% of whom were 24 or younger, 10% were 25 to 29 and only 4% were age 30 or older. This compared favorably to the group IV controls except for an increase in the number of 25-29 year olds. Though an exact tabulation of the ages of the population was not possible, the average age was definitely much higher with an estimated 35% being 25 years of age or older, but the range in age was approximately the same.

There were 28 cases of non-gonococcal urethritis that gave a history of sexual contact with only one female on one occasion for at least three (3) months prior to the onset of symptoms (24 of them had had only one (1) contact in five months or longer). Eight (8) were reportedly "virginal" contacts. The incubation period ranged from 5 to 63 days with an average of 22 days. Seventy-five percent of the cases occurred between the 9th and 30th days with the peak incidence in the 14-21 day period. Fourteen (14) of the 28 cases had a positive reciprocal complement fixation titer (32 or greater), and a similar case distribution curve and average incubation period as that of the whole group.

Serological Studies:

The serological results relating to each clinical group are summarized in Table I which shows the case distribution for each dilution of the CFT for the OA strain of TRIC. There were only five (5) patients (all in Group I) that showed any titer elevation to the LB₄ antigen at all and are as follows: 3 with a titer of 16 and 2 with 32 (all of which were initial titers and each decreased to < 8 on later specimens). Corresponding

TABLE I. Clinical Groups and Corresponding Ovine Abortion CFT results

Clinical GROUP	# of Cases	CFT Results								No. of cases with titer of 8 or greater
		<8	8	16	32	64	128	256	512	
I Non-gonococcal Urethritis, etc.	107	43	7	14	25	10	7	1	—	64
II Gonococcal Urethritis	51	25	3	5	8	4	4	1	1	26
III Asymptomatic Abacterial Pyuria	22	10	1	3	5	3	—	—	—	12
IV CONTROLS	283	241	6	10	19	3	3	1	—	42

GROUP No.	Total Cases	C.F. titer of 16 or greater		C.F. titer of 32 or greater	
		# of Cases	Percent	# of Cases	Percent
I	107	57	53.2%	43	40.0%
II	51	23	45.2%	18	35.3%
III	22	11	50.0%	8	36.3%
IV	283	*36	*12.7%	26	9.2%

*Further investigation of these cases revealed many of them to have pyuria (see text and TABLE II).

OA titers on all five (5) cases were < 8 initially and 3 of them increased to 16 (1 case), 32 (1 case) and 128 (1 case). An interesting point here was that the OA titer of 128 was in a case where the LB₄ titer was only 16. The peak of 128 was in the 4th week and had again returned to < 8 by the 9th week. Complement fixation tests using SA₁ and SA₂ strain antigens were also performed on several cases periodically, but no response was noted in the base titer (8) at all.

Group I: This group included 107 patients with a variety of problems as follows: epididymitis (3 cases), prostatorrhea (2 cases), Reiter's syndrome (1 case), intraurethral condyloma acuminata (1 case), and chancroid (1 case). The remainder of the patients were those with symptomatic non-specific urethritis and/or "prostatitis." Nineteen (19) of these cases denied having spots on their underwear; but either complained of being able to "strip a tear" from the urethra, or one was demonstrated during the exam-

ination. These latter cases, especially when associated with pyuria, are the ones that probably are given a diagnosis of "subacute" prostatitis and often are not considered significant enough to warrant treatment. The reciprocal C.F. titers were 32 or greater in 43 cases (40%) and 16 or above in 57 cases (53%). As will be seen later, the C.F. titers of 16 are often positive and therefore the percentage of positives at both the levels of 16 and 32 or greater will be included for convenience. (Note: All CFT's hereafter are for (OA) strain.)

Group II: There were 51 cases of Gonorrhea that met the criteria for inclusion in the serological portion of the study. 18 of these cases (35.3%) revealed a reciprocal titer of 32 or greater and at 16 there were 23 cases (45%).

Group III: This group was the smallest and included 22 cases of asymptomatic, abacterial pyuria which were discovered incidental to any sick call visit not related to the

TABLE II. GROUP IV CONTROLS: Ovine Abortion Reciprocal CF Titer Response Among Three Subgroups in Which ALL Subjects Had Urinalyses Performed in Addition to the Serological Tests.

Group IV: Controls Subgroups	No. of Cases	C.F.T.						
		<8	8	16	32	64	128	256
A. Physical exams: (Group, pre-radiation exposure)	53	43 (2)	—	4 (1)	4 (2)	—	2 (2)	—
B. All personnel in one Dept.	25	20	—	—	4 (1) *2	1	—	—
C. Cases with respi- ratory symptoms	**24	21 (1)	1	—	1	—	1	—
Total	102	83	1	4	10	1	3	—
(Pyuria)	(9)	(3)	—	(1)	(3)	—	(2)	—
NSU	*2	—	—	—	*2	—	—	—

() = number of cases with asymptomatic pyuria.

* = number of cases that developed NSU.

** = ten of these cases from a submarine were omitted due to no urinalyses being performed.

genitourinary system at any point proximal to the external urethral meatus. Three (3) of the patients had minimal pyuria and five (5) others could "strip a tear" when examined. There were eight (8) cases (36.3%) that revealed reciprocal C.F. titers of 32 or greater. Three (3) cases in this group had condylomata acuminata lesions and their corresponding C.F. titers are as follows: lesions of glans penis (1); solitary intraurethral lesion (1); and a complete perianal rosette (1) (extending up the anal canal to the ano-rectal line) with titers of 32, 32, and 16 respectively.

Group IV: The 283 patients in this group of controls were composed of essentially 6 subgroups. Three (3) of these with a total of 102 cases were evaluated the most extensively with a minimum of 2 sera 2-3 weeks apart (over 60% had a third serum collected at 5-8 weeks) and at least one urinalysis on all patients. Patients with asymptomatic abacterial pyuria occurring in this group were not included in Group III. The tabulation of the data on these 3 subgroups (102 cases) is given in Table II (the titer recorded with the highest on any specimen, and the figures in parentheses are the number of cases with pyuria, and those preceded by an

asterisk developed NSU during period of specimen collection). It is readily evident that 50% of patients with titers of 32 or greater either had pyuria or soon developed NSU. Also, considering only those cases with asymptomatic pyuria, both this group and the 106 cases in the next paragraph show comparable results (Table II). Of contrasting significance is the number of cases with pyuria and titers < 8.

Subsequently the occasion arose where a larger sampling of the study population could be done easily, with serum specimens collected coincidental with blood donations for the local blood bank of the British National Health Service. Of the 119 donors, 13 of them had been listed in one of the four clinical groups within the prior 6 weeks and were excluded. Among these 13 patients, one with NSU had a titer of 64, and the remaining 12 were in the Group IV controls with only one reactive titer of 16. The other 106 subjects revealed a titer response of < 8 in 95 cases (89.6%), and 11 cases (10.4%) had reactive titers which were as follows: 8 (1 case—pyuria found at 10 days with subsequent NSU and a titer elevation to 32); 16 (2 cases—1 with pyuria); 32 (6 cases—2 with pyuria); 64 (1 case—urine packed with pus

and shreads in the first glass, but he was asymptomatic). It is readily evident that 45.5% (5 of 11 cases) had pyuria or symptoms compatible with acute or subclinical urethritis—and furthermore, two of the others showed a transient, “equivocal” pyuria. The case with an initial titer of 8 was interesting in that it demonstrated the tendency toward an insidious onset of symptoms and a concomitant titer response.

Complement fixation tests were performed on 34 patients (24 aboard the HUNLEY and 10 aboard a nuclear submarine) in the control group with acute respiratory complaints to sample the study population for possible bedsonia respiratory illnesses. Influenza A and Adenovirus were responsible for over one half of the positive titers found in the men aboard the HUNLEY. A composite of the Psittacosis (OA) titers in both the HUNLEY and the submarine group are as follows: < 8 (30 cases); 8 (1 case); 16 (1 case); 32 (1 case); and 128 (1 case). There were 2 positive titers showing an incidence of

Complement fixation titer response: These results are best presented in the discussion portion for the optimal correlation of the findings.

Fluorescent Antibody (FA) Tests:

As a consequence of the previously mentioned problems with the FA test, any evaluation of these early results would be of equivocal value and certainly negatively weighted. For the sake of completeness those results are as follows: of the initial 29 patients studied, the FA test was considered positive on 10 of them, though only 1 of 3 smears were positive in some cases where multiple tests were performed.

The results obtained later from tests on 34 patients in Group I and 6 patients with asymptomatic pyuria in Group III are shown in Table III which equates the FA results to that corresponding C.F. titer. 23 of 34 cases of NSU and 4 of 6 cases in Group III were positive to either LGV or LB₄ or both, showing a total percentage of positive cases

TABLE III. Results of Fluorescent Antibody Tests and Corresponding Reciprocal C.F. Titers on 40 Cases (Group I = 34 Cases and the 6 Cases in Group III are enclosed in parentheses).

	No. of Cases	Reciprocal C.F. Titers					
		<8	8	16	32	64	128
Fluorescent antibody smears—POSITIVE	19	8	—	1	5	3	2
	LB ₄ (4)	(2)			(1)	(1)	
	LGV 3	1	1	—	1	—	—
	Both 1	—	—	1	—	—	—
Fluorescent antibody smears—NEGATIVE	11	8	—	—	2		1
	(2)	(1)				(1)	
Cases having either a positive FA smear and/or CFT	Group I	26	76.5%				
	Group II	5	83.3%				
	Total	31	77.5%				

5.9%. It is of interest to note that the case with the titer of 128 had positive results in six (6) of the ten (10) agents tested and also less significant responses to the other four (4) agents. Both the acute and convalescent sera reacted similarly (no explanation is offered for this hyperactive response).

to be 68% and 67% respectively. When only the LB₄ FA tests are considered, 56% of the Group I cases were positive. The correlation between this group of FA tests and the corresponding C.F. titers of 16 or greater is 56.5% (13 of 23) and at 32 or greater is 48% (11 of 23).

TABLE IV. Morbidity Findings: Groups I and II*

Clinical Evaluation	First Recurrence		Second Recurrence			Third Recurrence		
	Cases		No. of Cures	No Follow- up	Sx	Marked Pyuria	Pyuria Sx Only	
	No.	%						
Group I (107 cases):								
Treatment Failures:	32	20.5%	9	2	4	7	1	1
Symptomatic	12	11.2%	3	2	4	3	1	1
Asymptomatic Pyuria	10	9.3%	6	—	—	4	—	—
Group II (62 cases):**								
Treatment Failures:	19	30.6%	17	3	none	2	—	1
Gonorrhea	2	3.2%	2	—	none	—	—	—
NSU	9	14.5%	7	—	none	2	—	—
Asymptomatic Pyuria	8	12.9%	6	—	—	2	—	1

Treatment Failures	No. of Cases	C.F. Titer Results						
		<8	8	16	32	64	128	256
Group I	22	10	—	1	6	3	1	1
Group II	19	11	—	—	4	1	3	—

*Note: See text for data on other Morbidity—Epididymitis, Reiter's Syndrome, Prostatitis.

**11 additional cases included; see page 7, Group II Morbidity.

The intracytoplasmic inclusions met the criteria and description by Hanna¹⁰. Also, occasionally the area of fluorescence formed a crescent shaped cap adjacent to the nucleus.

Morbidity (and associated group findings):

The morbidity results, pertinent associated data, and several brief case findings are presented here by clinical groups. See Table IV.

Group I: Persistent or recurrent symptoms were noted in 12 patients (11.2%): dysuria (3 cases) and urethral discharge (9 cases—2 of which persisted for more than 8 days while receiving treatment.) Some very interesting findings were noted among the symptomatic failures:

a. Following the second treatment of these patients there were only 3 cases that could be considered "cures"; 2 cases were transferred and lost to further follow-up; 3 continued to have marked pyuria; and within a range of 25 to 35 days a **second** recurrence of a urethral discharge developed in 3

cases, and the one (1) remaining case was admitted to sick bay with acute epididymitis. (Two (2) of the cures were in both patients with the "persistent" urethral discharge.)

b. A third round of problems also occurred in two (2) of the three (3) subjects who had had second recurrences of the urethral discharge; one (1) as asymptomatic pyuria (marked) and the other as a third recurrence of the discharge—again on a "4 week cycle." The **former** case always showed pyuria in the first glass urine to some degree, but never clinical or laboratory evidence of prostatitis. Reciprocal C.F. titers revealed an initial increase from < 8 to 32, and then at the time of the second recurrence in the 8th week it had gradually returned to a level < 8, (where it remained). The **latter** patient with the 3rd recurrence of the urethral discharge always had a normal urinalysis at 2-3 weeks after treatment, but concurrently revealed an abnormal prostate to palpation and secretions that were loaded with WBC's

and also clumps. He gave a history of new sexual contacts prior to two of the three recurrences. With each episode of symptoms the reciprocal C.F. titer progressively peaked higher to a level of 256 before it eventually returned to 16 subsequent to a case of gonorrhea (12 weeks after NSU).

c. Without exception, the symptomatology in each case became progressively less severe in successive recurrences.

d. The recurrences also appeared to follow a 4-5 week cycle rather consistently and occasionally showed a similar "cyclic variation" in the amount of pus in the urinalyses of some cases with asymptomatic pyuria.

Persistent or recurrent asymptomatic pyuria occurring in ten (10) patients (9.3%) was considered to be clinically significant, and they were given additional treatment. Two (2) of these cases had developed findings of prostatitis after their initial prostate examination had been considered normal, and one (1) patient was found to have a solitary intraurethral condyloma acuminata on a subsequent office examination. Considering these 22 cases as the "treatment failures," then the overall rate was 20.5% and eleven (11) of them had reciprocal C.F. titers that were 32 or greater and thirteen (13) were 16 or greater.

There were an additional 12 patients with minimal pyuria in the asymptomatic group and in whom treatment consisted of the basic studies for exclusion of serious genitourinary disease and then periodic clinical and laboratory evaluation. Most of these had cleared by 6 weeks, but a few revealed variable pyuria, equivocal to 1-Plus, occasionally. Only two (2) of the subjects were found to have a C.F. titer of 32 or greater. Three (3) cases had mild pyuria at the time they were transferred, and subsequently lost to follow-up.

General remarks: The recurrence of symptoms most frequently occurred between the 3rd and 5th weeks (21-35 days) following treatment in all but one of the "symptomatic failures;" and in the "asymptomatic failures," moderate to marked pyuria was often prominent on the first follow-up urinalysis

(10-14 days), or at 4 weeks. Over 50% of the urine specimens were "initially" negative by the end of the 3rd week.

It is clearly evident that once a patient had developed a recurrence of the urethral discharge, there was a **MARKED** tendency toward chronicity and most patients were treated with several chemotherapeutic agents. The ones that "recurred" only with pyuria did not show this chronicity, and no case developed symptoms that were more severe than their preceeding complaints.

Urological consultation for further evaluation and treatment was obtained on three (3) patients in Group I; two (2) cases with marked, persistent pyuria, and one (1) with an intraurethral venereal wart. Fulguration of the wart was done and the reports gave the findings as "urethritis (and/or prostatitis) resolving," but no other description was provided regarding the endoscopic findings.

Group II: In addition to the 51 cases of gonorrheal urethritis included in the serological portion of the study, there were eleven (11) other cases that failed to meet the stated criteria and were excluded, (i.e., 3 cases were due to being transferred in less than ten (10) days, and eight (8) cases developed gonorrhea within 4 to 10 weeks after having NSU in Group I). These patients are reincluded for completeness of the morbidity and bacteriological results and this brings the total to 62 cases for evaluation. Though one might think morbidity statistics would have become worse by adding these recent cases, there was actually a slight improvement.

A recurrent urethral discharge occurred in eleven (11) cases (17.7%), nine (9) of these cases (14.5%) had non-specific urethritis and two (2) cases (3.2%) had gonorrheal urethritis proven by two (2) smears and two (2) cultures. The recurrences with NSU usually occurred during the 2nd or 3rd week (6 of 9 cases), but three (3) were at 5, 6, and 8 weeks. As usual, the interval for recurrences of gonorrhea was quite short (3 and 4 days after treatment for each case).

Eight (8) cases were given further treatment for asymptomatic persistent pyuria. Very significant amounts of pus were nearly always noted to be present at 14 to 21 days and when the pyuria occurred this early following treatment, it usually became worse or remained status quo rather than improving as in other cases. This was evident since treatment had not been started in some cases for as long as 5-8 weeks.

It was rather common to find mild pyuria in urine specimens around ten (10) days and even though most of these were clear by the 4th week, they were always reevaluated closely.

Including all recurrent cases and persistent pyuria requiring treatment, 19 of 62 cases were considered "treatment failures,"¹¹ and they gave a 30.6% failure rate.

The results of the CFT's were taken from only the 51 cases previously stated acceptable subjects. (However, when all 62 patients were included, there was essentially no change in any of the computations.) Positive CFT's were noted in 3 of 9 cases of recurrent urethral discharge and 3 of 6 cases with asymptomatic pyuria requiring treatment, giving an overall 40% incidence of positive titers. There were no titers at the level of 8 or 16, and the case responses were: 32 (3 cases); 64 (1 case); 128 (2 cases). This is certainly a higher "overall" level of C.F. titer distribution than has been usually seen in other groups.

There are several interesting points that can be seen in reviewing the results tabulated for this group in Table IV and other compiled data.

a. It is readily apparent that the recurrence of a discharge following gonorrhea does not carry the same statistical significance as it did in Group I cases—there were no cases who developed another discharge following treatment of the first recurrence, and only two (2) who had persistent pyuria requiring further treatment.

b. It was obvious as the patients were being seen and when their charts were reviewed later that they required less follow-up

than the average NSU patient did for chronicity.

c. There were two (2) cases that were evaluated as Reiter's Syndrome in this group. They are presented as a separate topic with a third "typical" case from Group I and are not tabulated in the morbidity results in Table IV.

Group III: Of the 22 cases of asymptomatic pyuria ten (10) of them with a minimal to mild amount of pus were not given any specific treatment—their urines cleared in 2-4 weeks (often less) and remained so. Treatment was given to the remaining 12 cases with persistent pyuria of 15-20 WBC's/HPF or more, and nine (9) of these were considered "cures." Reports on the failures are as follows: a. One (1) case, originally found to have mild pyuria, developed recurrent marked pyuria five (5) weeks after his urine had previously cleared. All his C.F. titers were < 8 except the last one which was 8. He was subsequently lost to follow-up and treatment which was started just before he was transferred. This case probably experienced a reinfection. b. Each of the other two (2) cases with persistent or recurrent pyuria following treatment had condylomata acuminata—one intraurethrally and one with a rosette of perianal warts extending up the anal canal nearly to the ano-rectal line. Their respective C.F. titers were 32 and 16.

Prostatitis: It was thought that a fair number of these cases would reveal definite signs of "subacute" prostatitis. One or more prostate examinations were conducted in 16 cases though patients with mild pyuria sometimes were not checked. One (1) of them revealed definite clinical and laboratory evidence of prostatitis and three (3) cases had inconclusive signs; i.e., two (2) with equivocal bogginess, but normal secretions and one (1) with a normal gland to palpation, but 20-25 WBC/HPF.

Slight induration in the region of ampulla of the vas was found either unilaterally or bilaterally in five (5) additional cases and in one (1) of the above cases. Little if any change was noted between examinations and the prostate secretions were all normal (the

two (2) cases with the greatest amount of pus revealed 10 to 15 WBC's/HPF and no clumps). The results of secretion examination or 3rd glass urine specimens were not specifically recorded in eight (8) other cases except as a "normal prostate" notation on the chart.

Submarine (FBM) Group: There were 18 cases of NSU and five (5) cases of gonorrhea occurring in patients assigned to Fleet Ballistic Missile (FBM) submarines. Though the results of these patients have been included previously, they are again presented separately for their interest with regards to the morbidity findings. The control of personnel movements were even more stringent in this group. After about four (4) weeks moored alongside the tender, USS HUNLEY, they would deploy on patrol and spend approximately the next eight (8) weeks submerged and completely isolated. Symptoms appeared during patrol or the ten (10) days prior to deploying in nearly 50% of cases. Nine (9) cases in unmarried men had had sexual contact with only one (1) female in the prior three (3) months, and of the three (3) married men, only one (1) admitted extramarital contact. Complement fixation titers were 32 or greater in six (6) cases (33%) and 16 or greater in eight (8) cases (44.5%) in the 18 patients with NSU. Two (2) of the five (5) cases of gonorrhea had titers of 32.

There was **minimal** morbidity among this group when compared to the remaining 89 cases of NSU in Group I. The one symptomatic failure (5.5%) was in a patient whose discharge rapidly improved on treatment, but he continued to complain of "a morning tear" for eleven days. No further treatment was required, and his urine was clear at the end of patrol. One additional patient returned from patrol with mild pyuria (10-15 WBC/HPF), but was asymptomatic and no treatment was given. Also all five (5) patients with gonorrhea remained asymptomatic and had negative urinalyses at the end of patrol.

Equivalent statistics in the 89 other patients revealed: 11 cases (12.4%) with re-

current symptoms (7 of whom developed one or more additional recurrences); 10 cases with persistent pyuria requiring treatment (11.2%); and 11 cases not needing treatment (12.4%).

Epididymitis:

Epididymitis is another complication of non-specific urethritis^{30, 32} and the four (4) cases occurring during this study are presented as a separate topic. Two (2) of these acute cases occurred without a recent history of venereal disease or other genitourinary symptoms, but clinical and laboratory findings of prostatourethritis were clearly evident on the initial or subsequent examinations. The reciprocal C.F. titers were positive in both cases with an increase during the convalescent period to a level of 64.

A third patient was initially seen with mild transient dysuria and moderate pyuria (35-40 WBC/HPF) in the 1st glass specimen; but because the symptoms rapidly disappeared spontaneously, he did not return to sick call as directed. When he was eventually seen at three (3) weeks and again at six (6) weeks, 2 glass urinalyses were entirely negative; however, five (5) days after the last specimen was collected, he was admitted to sick bay with an acute left epididymitis and a mild pyuria. He denied any previous sexual contact except for one occasion approximately three (3) weeks prior to the onset of his initial symptoms. His reciprocal titer response was from a level < 8 to 16, (serums followed only 7 weeks).

The fourth case occurred in a patient who initially received treatment for NSU (oxy-tetracycline), but developed a "recurrence" of the discharge on the 26th day after starting treatment. These symptoms "were so mild" (lasted 24 hours) the patient ignored them and did not seek medical attention again until he presented acute right epididymitis four (4) weeks later. He was admitted to sick bay for treatment, following which he remained asymptomatic, with clear urine until seven (7) months later. At that time he was again admitted with a urethral discharge and right epididymitis. This episode failed to respond as well as the previous one,

and a mild tenderness and epididymal induration persisted for approximately six (6) weeks.

The reciprocal C.F. titer was also interesting in this case in that it revealed peak titer elevations to the next higher levels (32, 64, 128) in the 3rd or 4th week after each successive "recurrence or reinfection." Following each peak the level decreased to 8, approximately 6 to 8 weeks post treatment. The peak titer of 128 in the 3rd week after onset of his 2nd case of epididymitis, was probably the result of a reinfection. This was not recorded as a "new case" though it met the previously described criteria to consider it as such.

Reiter's Syndrome:

The findings and brief histories of three (3) cases having Reiter's Syndrome, or suspected of having a clinical variation of this condition, are presented here. It is significant to note that each of them had increasing and/or decreasing titers at positive levels; 32 in two (2) cases, and one (1) case had the highest level recorded in the entire study, a reciprocal C.F. titer of 512.

The typical triad of conjunctivitis, urethral discharge, and arthritis was present concurrently in one (1) case. The conjunctivitis was mild and bilateral and the non-specific discharge followed penicillin treatment for gonorrhea the week previous. Joint symptoms consisted of idiopathic pain and some effusion in the left knee, and an arthrocentesis was considered necessary a week later. Approximately three (3) weeks from the onset, he was again seen with a mild unilateral recurrence of the conjunctivitis and a week later idiopathic pain in his right foot was sufficient to require admission to sick bay for five (5) days. A slight amount of pain had persisted in the left knee. Several urinalyses during this period had all shown a persistent mild to moderate pyuria, but he was never given additional chemotherapy. There was no further recurrence of symptoms during the subsequent five (5) months of follow-up.

The second case was seen originally for gonorrhea (which rapidly cleared with peni-

cillin), but continued to have 20-25 WBC's and 8-12 RBC's at the end of eleven (11) days. A prior specimen had revealed "numerous WBC's and RBC's." Further investigation did not reveal evidence of N. gonorrhea, and during the 2nd to 3rd week (from onset of gonorrhea) he was seen for "recurrent" idiopathic pain and effusion in his right knee. The first episode had occurred six (6) weeks previously (i.e., 3 weeks prior to gonorrhea) and resolved spontaneously except for occasional slight pain. Subsequent admission to the Air Force referral hospital for orthopedic and urological evaluation failed to reveal any definitive diagnosis regarding the problem with his knee or for the hematuria. During the 6th week, he was seen with a slight pustular exudate in the right eye and only mild ocular symptoms. The palpebral conjunctiva was markedly injected bilaterally and the reaction appeared to be out of proportion to the symptoms and the mild hyperemia of the bulbar conjunctiva of the right eye. He also stated he had had similar symptoms during the prior month, but were so mild he never mentioned them to anyone. The effusion in his right knee had also progressed, and an arthrocentesis produced over 60 cc of clear, serous fluid. He became asymptomatic without further treatment, and a moderate pyuria was last noted during the 7th to 8th weeks with several subsequent urinalyses being entirely negative. A "recurrence" of mild pain in the knee was elicited during the 12th to 13th weeks, but no effusion was present, and no other problems developed during the next three (3) months prior to his being transferred. Briefly, the reciprocal C.F. titer response was: initially positive at 64; increased to 512 by the 9th week; decreased to 32 in the 17th week; and was essentially the same at 26 weeks.

The third patient presented with idiopathic pain and effusion of the left knee as the only findings—except for a rising C.F. titer from <8 to 32. This man originally had a titer of 32, when seen with NSU and was one of the group from whom serum specimens were being collected more frequently to study the titer response. At the 8th week following

TABLE V. Findings on Prostate Examination and Correlation to CFT Results.

		Reriprocal CFT				Recurrent Symptoms	Persistent Pyuria
		No. of Cases	8 or less	16	32 or greater		
41 Cases	only one exam	16	9	1	6		1
Initial exam	2 or more normal exams	15	9	1	5	3	2
normal	Became abnormal later	10	2	—	8	5	2
28 Cases	one exam only	6	3	1	2	1	
Abnormal	Improved	8	3	2	3		
or equiv. abn. exam	Became worse	5	2	1	2		2
	No change	9	4	1	4		3

the onset of NSU, a urinalysis was noted to have 30-35 WBC's/HPF, but no treatment was started. The urine then became clear and the titer decreased to <8 at the 13th week. It remained at that level for four (4) consecutive weeks, and during the 17th week the joint symptoms first appeared for no apparent reason. Two (2) weeks later the titer was again elevated to 32, and it remained at this level for three (3) weeks until it again reverted to <8 by the 25th week. The urine also remained negative after the joint symptoms resolved spontaneously, and no evidence of conjunctivitis occurred.

The first two (2) cases presented were quite promiscuous sexually, but the last case had had only two (2) different contacts.

Fluorescent antibody smears were not obtained in the first case, and in the second, the F.A. smears had been temporarily discontinued at the time his ocular symptoms occurred. A positive urethral F.A. smear was reported during the original episode of NSU in the third patient, but no subsequent smears were collected.

Prostate Evaluation:

An attempt was made to evaluate the relationship between NSU and prostatitis. Initial prostate examinations were done on 69 cases in Group I and 47 of them received one or more follow-up exams. Using the results of the first examination, they were divided into two (2) major groups: one with "normal" prostate glands (41 cases), and the other with "abnormal" (or equivocally abnormal) glands

(28 cases). Since no massages were done in the presence of acute urethritis, the grouping was determined by the palpatory findings and without knowledge of the C.F. titer reports. In the former group, there were ten (10) patients who later developed abnormal prostate findings, and the other 15 cases with persistently normal glands were grouped with the 16 subjects in whom the initial examination was normal, but no other exams were done. Of the 28 cases with initially abnormal findings, six (6) patients definitely became worse and eight (8) were considered to improve during the following 6-8 weeks. Three (3) of the eight (8) with improvement returned to "normal" and had lost all evidence of any induration.

The comparative C.F.T. distribution and morbidity results occurring in these 69 patients are shown in Table V and some interesting findings are readily seen:

a. Nearly all the symptomatic recurrences occurred in the group with "initially normal" prostate and were uncommon in the "initially abnormal" group, but asymptomatic pyuria was slightly more prevalent in the latter group.

b. A patient with a normal prostate who subsequently develops findings of prostatitis will also probably have a positive C.F. titer to TRIC and have a recurrence of symptoms at least once.

c. The overall number of titers 32 or greater were fairly comparable in both groups and any attempt to accurately "predict" the

titer response during the initial visit was quite frequently erroneous, even in the "most typical" NSU cases. However, in obvious cases such as the patients with prostaticorrhea (3), chancroid (1), and in 5 of 6 married men who denied extramarital sexual activity, there would have been a 9 in 10 chance of predicting a "negative titer." Except for these rather evident choices, any speculation regarding the titer response was soon shown to be very inaccurate and any further attempt to establish a "titer-symptomatology" pattern was abandoned.

d. Residual induration in the region of ampulla of vas was ultimately the most common persistent finding in the "normal-to-abnormal group," once the pus in the secretions had cleared. It usually remained for at least 3-4 months (or longer), though in one case it cleared within 4-5 weeks.

e. A review of charts showed that two (2) patients who were among the most difficult to cure never revealed any abnormal prostate findings on any of several examinations.

Bacteriological and Other Studies:

The bacteriological evaluation of urethritis presented some interesting facets that shall be reported in more detail in a separate communication dealing with gonorrhea (including 46 additional cases) and other possible causes of "primary bacterial urethritis." Briefly, the most important observations were: (1) A much lower incidence of recurrent gonorrhea than often reported in some studies in recent years, but compares favorably with the results given by Smith (1966)²⁶; (2) The diagnosis of non-gonococcal bacterial urethritis, either of primary origin or secondary invasion by a bacterial "opportunistic," was suspected when intracellular organisms of similar morphology were found on 2 or more daily gram stained smears. These findings were present in less than 10% of the cases reviewed and a positive C.F. titer response was later noted in over 50% of them; (3) Additional findings of interest were 2 cases that did not reveal N. gonorrhea until the 2nd and 3rd daily urethral smears were obtained and of special note were 2 patients

found to have gonorrhea without the presence of any urethral discharge. The latter cases presented with only dysuria which was very mild in one and moderate in the other. (Pyuria in the 1st glass specimen was noted in both instances). In the above situations confirmatory smears and cultures were usually repeated prior to starting treatment later the same day or the following morning.

"T-Strain" PPLO: An unsuccessful attempt was made to culture this organism from the urethral discharges of 20 patients at the midpoint of this study. The failure was probably due to a variation in technique from that used by Shepard. Since it was not practical to send each patient to Belvedere Hospital so that direct inoculations could be made, the specimens were initially inoculated into a PPLO broth, which was later transferred to the testing laboratory. No other trials to grow the organism were made.

DISCUSSION AND CONCLUSIONS

The cooperation of most of the patients was outstanding and was definitely a major contribution to the collection of reliable and useful data in this study. Additional impetus for some patients to return to sick call for the frequent collection of laboratory specimens was due to their own curiosity and/or concern regarding an elevation of their C.F. titer to TRIC, and a few undoubtedly kept their appointments only when their workload was heavy. The responsiveness in many cases was probably attributable to the fact that time was **always taken** to give each patient a "personalized enlightenment," regarding the aspects of venereal disease during each of several initial interviews and/or sick call visits. The lectures always included a brief layman's description and explanation of their disease process, what to anticipate, and the necessity for post treatment laboratory studies to assure that the disease was indeed cured. There were 43 cases (24 with NSU and 19 with G.C.) that were followed for more than three (3) months and over one-half of these for six (6) months or longer; some for recurrent problems, but in most cases it was for an elevated C.F.T.

C.F. Titer Response and Related Findings:

Some of the most significant facts related to the study are associated directly or indirectly with the C.F. titer response among the various case groups, as compared to the clinical aspects of the disease process. These results are compiled in Tables 6 (a), (b), (c), and (d), and the overall group tabulations have been shown in Table 1. A few individual case responses and the results of the only five (5) cases with any titer response at all to the type specific LB₄ antigen have been previously presented. As seen in Table 1, there were

64 patients (60%) in Group 1 and 26 patients (51%) in Group II, who had at least a minimally "reactive" CFT during the first few weeks, either as an initial or delayed response.

C.F.T. Results:

Group 1: The individual titer responses in 27 cases in this group revealed the acute serum specimens to be "non-reactive" at any dilution; and later showed a titer of 8 or greater to Ovine Abortion antigen. The distribution and levels of the first recorded titer responses, as a function of time in weeks

TABLE VI(a). Time of appearance and level of first OA titer response (from the onset of symptoms) among 27 cases with initially non-reactive CFT.

CFT	Week from onset of symptoms								Total cases each CFT level
	1	2	3	4	5	6	7	8	
8	1	1	1						3
16		5	2	2	1	1	1		12
32	1	3	3	1					8
64	1		3						4
128	—	—	—	—	—	—	—	—	0
Total cases by weeks	3	9	9	3	1	1	1	—	27

TABLE VI(b). Time of occurrence of Peak Titer response among the same cases in Table VI(a).

CFT	Week from onset of symptoms								Total cases of each CFT level
	1	2	3	4	5	6	7	8	
8	1		1						2
16		2	1	3	1	1			8
32		1	4	3		1			9
64		1	3					1	5
128		2	1						3
Total cases by weeks	1	4	11	7	1	2	—	1	27

TABLE VI(c). Cases in Group I found to have a reactive titer on the initial visit to sick call. (Distribution of 37 cases at the various C.F.T. levels).

C.F.T.	No. of Cases			
	Initial titer level	Titers remaining status quo	Peak titer level	Last or lowest titer recorder after peak
<8	—	—	—	17
8	6	2	4	6
16	13	3	6	8
32	16	2	17	3
64	2	2	5	3
128	—	—	4	—
256	—	—	1	—

from the onset of symptoms, are given in Table 6 (a); and a similar tabulation of the "peak" titer levels are shown in Table 6 (b). It is readily seen that the first titer response occurred by the 3rd week in 21 cases (78%) (three (3) had slight titer elevations at 7 days). The highest titer usually appeared shortly thereafter, with the most frequent peak in the 3rd week (12 cases, or 44.5%), and 22 cases (81.5%) occurred during the 3rd and 4th weeks. Following treatment, 17 of the titers reverted to <8 over a wide range of time (3 to 13 weeks with nine cases), with the rest of the cases spread evenly from the 6th through the 9th weeks. Eight (8) of the remaining patients revealed titer responses of 8 (1 case), 16 (6 cases), and 32 (1 case) on their last visit during the 9th week or later. (Three (3) of them had been followed for 15 to 24 weeks). As one would expect, the cases with the highest titer levels were the ones that persisted for the longest period and those developing peak titers at five (5) weeks or later also persisted longer. Two cases were transferred.

Pertinent data on the 37 cases with "initially reactive" sera in Group I is shown in Table 6 (c). It is self-evident that even though these titers start with an elevation, a significant number of them continued to increase (14 cases); nine (9) showed essentially no change (two (2) of which were followed for only 2 to 5 weeks); and the remainder were at their "peak" and began to decrease. Four (4) of these latter cases had previously been in the "control" group and had been found to have a titer of 8 or <8 at 2 to 4 weeks prior to developing symptoms. As compared to the patients in the previous group with "initially non-reactive" titers, the "peak" elevation occurred approximately 1 to 2 weeks later in the 14 cases where the titer continued to increase. The duration of the titer response prior to reverting to negative was also significantly increased. Only 12 cases at 10 weeks and 14 cases at 13 weeks had titers of <8 , and there were an additional four (4) cases with a titer of 8.

Group II: A C.F. titer response was demonstrated in the acute sera of 16 patients in Group II, and ten (10) others had a delayed

response. It was noted that the percentage of cases with initial or delayed titers in both Groups I & II were essentially comparable. In contrast to non-specific urethritis, the increased severity of symptoms with gonorrhea almost invariably caused those patients to seek medical attention much earlier, and it would follow that the serological response to TRIC agents, (in the event of a concurrent infection) would **probably not** be a prominent finding initially in this group. **However**, contrary to prior reasoning, there was a greater proportion of the acute sera with positive C.F. titers in the gonorrheal group—ten (10) of the 16 initially reactive titers (62.5%) were 32 or greater, while only 18 of 37 (48.7%) of the NSU group were positive. Further evaluation of the 16 cases with reactive titers also revealed other unexpected findings. In the ten (10) cases with initial titers of 32 (8 cases) and 64 (2 cases), five (5) of them increased to very high levels, not commonly seen in such a small group of subjects.

a. Only one (1) case (titer of 128) was uncomplicated. The remainder of the peak titers were: 512 (1 case) with probably Reiter's Syndrome), 256 (1 case) and 128 (2 additional cases).

b. Among the other five (5) cases the titers remained relatively stable for 3 to 5 months at 64 to 32 (1 case), 32 (2 cases), and 32 to 16 (2 cases) and only one (1) of them required treatment for pyuria.

c. In contrast to the rather high and persistent titer levels in the above cases, four (4) of the remaining six (6) patients (all with titers of 16) showed a "step-wise" decrease on weekly CFT's to 8 and subsequently to <8 during the 4th to 6th weeks—titers such as these should be considered as evidence for concurrent (or prior) NSU which is resolving. The titer of one (1) case increased to 32 and persisted there for 14 weeks before reverting to <8 at 16 weeks, and has been previously presented as a possible "atypical" Reiter's Syndrome.

"Initially non-reactive" Group II cases often revealed that the first titer demonstrated was also the "peak" response and occurred earlier than in the comparable set of

cases in Group I. Six (6) patients subsequently developed titers of 32 or greater and four (4) of them reverted to negative in 9, 13, 14, and 18 weeks respectively. Only the two (2) that cleared in 13 and 14 weeks required further treatment for NSU that developed at 2 and 5 weeks respectively. The titer on the latter case was still < 8 at 5 weeks.

CFT's on Special Cases: The cases that yielded some of the most interesting and informative data concerning the C.F. titer response were those patients in the Group IV controls who subsequently developed symptoms of urethritis a few weeks later. There were seven (7) such cases (5 with NSU and 2 with G.C.), with one (1) or more titers of < 8 (5 cases) and 8 (2 cases) reported within 2 to 5 weeks prior to the onset of symptoms. All seven (7) of the acute sera subsequently revealed titers of 32, and one (1) of them continued to a level of 128 following treatment. Five (5) of them had reverted to negative within a period of 6 to 13 weeks and the other two (2) cases were only followed for less than 5 weeks.

In a few of the cases that had reverted to negative, but continued to have periodic sera and urinalyses collected, it was noted that their titers would gradually become elevated to the previous level or occasionally higher, and later decline to negative again within 6 to 12 weeks. Nearly all of them revealed a minimal to moderate transient, asymptomatic pyuria not requiring treatment, and an occasional patient would have several clear urinalyses.

Discussion and Conclusions:

In the opinion of the author and others²⁰ it is evident that urethritis due to "TRIC Agents" of the bedsonia group of organisms is definitely more common than previously considered and probably accounts for the "lion's share" of the cases of "non-specific urethritis." Also, the fact that more than one of these organisms may be a causative agent is manifested by the "serological disappearance" of the LB₄ strain (last positive case in May 1965), without a significant change in the incidence of NSU and with the OA (group antigen) continuing to be positive

as before. However, this may well be attributable to the organism's ability to change its antigenicity. It has been noted that the fluorescent antibody tests for the LB₄ strain continued to be positive even with negative LB₄ C.F. titers. This may be evidence that the F.A. tests may show even more "cross reactions" among antigenically similar strains than is seen with the CFT's. The significance of one (1) of the five (5) cases with an LB₄ titer response revealing a level of 16, while the corresponding O.A. "Group antigen" was 128, is another unexplained complexity. It is unfortunate that attempts at isolation of the "current strain" were unsuccessful and also that more cases did not show an LB₄ titer response to further evaluate the possibility of antigenic change.

A rather detailed C.F. titer response has been presented and many of the corresponding relationships between the clinical aspects and the titer can be explained by: (a) in the bedsonia group, one (1) of the predominant host—parasite relationships is LATENCY^{33, 38} etc.; (b) the "coexistence of latent infection and antibodies is typical" of these agents³⁸; and (c) the discussion of the immune mechanisms of viral infections by Fenner³³—especially the "primary" and "secondary" antibody responses to replicating antigens. Basically, the primary response to the host's initial exposure to the disease shows the production of a **limited amount** of antibody following the inductive phase, and a "pure response" is difficult to obtain. Also, "tolerant animals" may even fail to produce any detectable antibody titer. After subsequent exposures, the secondary response is characterized by: (a) a shorter induction period (initial CFT's may be reactive); (b) production of larger amounts of antibody; and (c) a slower rate of decline of antibody synthesis.

It has been shown that the C.F. titers were elevated on the initial visit in many cases. This could be explained possibly as an example of a "secondary antibody response"—but may well reflect the insidious nature of the disease process in some cases. Occasionally a patient with pyuria would develop urethritis symptoms and a positive C.F. titer one to several weeks later.

The best example of latency and the tendency for inapparent infection is seen in Group III cases with asymptomatic abacterial pyuria, and also among the Group IV controls examined because of a "reactive" CFT and found to have a high incidence of pyuria. This could only mean that a large number of cases go unrecognized—possibly 10-20%. Coupled with the fact that there are few if any symptoms produced in the female, the problem of controlling the disease is self evident.

What C.F. titer level for TRIC agents should be considered "positive"? Can the test for the "group antigen" be utilized as a diagnostic procedure? In reply to the first question, it is the opinion of the author that titer levels of 16 are often positive; and even some at lower dilutions, when all the clinical aspects have been evaluated. The subtle rise and fall in titers can often only be detected if serum specimens are collected much more frequently than the routine "acute and convalescent sera" usually utilized. Also, many cases probably require repeated exposure before a titer rise occurs to an "arbitrary level" generally considered positive. This has been demonstrated experimentally in animals to some extent by Murray and others.

With regards to the second question—yes, the "group antigen" CFT can be useful in the diagnosis of a specific disease process caused by an agent in that group, if certain criteria are met: (1) One must have current knowledge regarding the incidence of reactive titers among the subject population, (2) The presence of symptoms and/or findings compatible with the diagnosis of the disease in question, and (3) Clinical evaluation to help rule out the possibility of the reactive titer response being due to another agent in the group. (A CFT for TRIC agents is certainly not recommended for the diagnosis of TRIC Urethritis among workers in a poultry processing plant!)

Isolation of the organism would only give the diagnosis in "retrospect" and not really assist in the immediate clinical evaluation of any case—and in addition, TRIC agents have been very difficult to isolate in the past. This leads to the subject of fluorescent antibody studies as a diagnostic aid. Though there

were technical difficulties encountered with the tests early in this study, the later results were more impressive. It is definitely felt that this is the procedure to use in the diagnosis of TRIC urethritis. As the methods for preparing better reagents (antisera) improve, it will probably become the most reliable diagnostic procedure for both the latent and symptomatic forms of the disease.

In an evaluation of the morbidity findings, it was shown that "chronicity" was not as prevalent in those cases of NSU that occurred concurrent with, or subsequent to Gonorrhea. The reason for this is not evident, but the sequential use of antibiotics may be beneficial as is recommended in the treatment of another venereal disease in the Bedsonia group, Lymphogranuloma Venereum. It is possible that the Penicillin used in the treatment of the initial case of Gonorrhea also affects the TRIC agent in its maturation phase, making it more susceptible to the tetracyclines.

The lack of complications among the cases occurring in patients stationed aboard the nuclear propelled Fleet Ballistic Submarines is worth reemphasizing. Though there were only 25 cases of venereal disease reported from this group in the study, by personal experience and/or communications with other Submarine Medical Officers over nearly a 4 year period, the additional information seemed to further substantiate this decrease in morbidity. Two suspected reasons for this are brought to mind since the submarines remain submerged for about 2 months; and (2) As shown by Schaefer in his experiments with prolonged exposure to elevated levels of carbon dioxide (1.5% for 42 days), the resultant physiological change (a mild respiratory acidosis that becomes compensated around the 24th day of exposure) causes a decrease in the urinary pH and an increase in bicarbonate excretion. Though reinfection is suspected of being the basis for the different morbidity results, there still remains the fact that a change in urinary pH has been an acceptable method of treating "chronic urethritis" in the past. However, since the average atmosphere level of CO₂ in SSBN's on patrol usually is less than that used in "Operation Hideout," it is not en-

tirely certain that the lower CO₂ concentration would cause a change comparable to that described. To my knowledge there has not been a similar study done on SSBN's while in an operational situation—the results would be interesting.

In addition to the "cyclic, monthly recurrences" (or reinfections), there are several other recognized complications of NSU; venereal prostatitis, epididymitis ("non-specific"), and an increasing number of reports associating Reiter's Syndrome with the disease. Of these conditions epididymitis affecting young adults is quite common in the Navy and (with the exception of wartime casualties) is ranked with pilonidal cysts as the two most common causes of "lost time" illnesses. During a 5 year period in the latter part of 1950's there were approximately 900 cases of epididymitis admitted to the U. S. Naval Hospital, San Diego, and the average hospital stay was in excess of 2½ weeks. The latter complications do not commonly occur in cases of adequately treated NSU. This adds to the author's belief that the latent and inapparent infections showing only asymptomatic abacterial pyuria should be treated as vigorously as is the acute form of the disease. "First glass" pyuria in young adults should be treated as "NSU" until proven otherwise. In Russia, Zade³⁰ reported a 4% incidence of epididymitis following NSU. However, urethroscopy was always included in the post treatment follow-up, and this high occurrence is probably secondary to the instrumentation. In the author's opinion TRIC agents will eventually be shown to be the major etiologic organisms in epididymitis in addition to "NSU."

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<p>The relationship between Trachoma-Inclusion Conjunctivitis agents (TRIC Agents) and Non-Specific urethritis (NSU) was investigated. The results of complement fixation and immunofluorescence studies using a "group" and a "type-specific" antigen/antiserum are presented in detail, as well as other associated clinical and laboratory findings related to a routine evaluation of urethritis. It was shown that one or more TRIC agents probably account for a much larger percentage of "NSU" cases than previously thought. There appears to be a definite interrelationship between TRIC urethritis and epididymitis in young adults, and possibly with Reiter's Syndrome. Further investigation of these relationships should certainly be done. (A protocol for such a study to be conducted at USNH, San Diego is being prepared for submission.)</p>			

14.

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NAME	ROLE
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Abacterial pyuria in NSU